Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Indomethacin

Indocid, Indocid retard, Inacid, Inacid Retard, Chrono-Indocid

FI/W/006/pdWS/001

<table>
<thead>
<tr>
<th>Rapporteur:</th>
<th>Finland (FI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finalisation procedure (Day 90):</td>
<td>2.3.2015</td>
</tr>
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### ADMINISTRATIVE INFORMATION

<table>
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<tr>
<th>Invented name of the medicinal product:</th>
<th>See section VI</th>
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<tbody>
<tr>
<td>INN (or common name) of the active substance:</td>
<td>indomethacin</td>
</tr>
<tr>
<td>MAH:</td>
<td>See section VI</td>
</tr>
<tr>
<td>Pharmaco-therapeutic group (ATC Code):</td>
<td>M01AB01</td>
</tr>
<tr>
<td>Pharmaceutical forms and strengths:</td>
<td>capsule, 25 mg prolonged-release capsule, 75 mg suppository, 50 and 100 mg</td>
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</table>
I. **EXECUTIVE SUMMARY**

No SmPC and PL changes are proposed.

**Summary of outcome**

- No change
- Change
- New study data: N/A
- New safety information: N/A
- Paediatric information clarified: N/A
- New indication: N/A

II. **RECOMMENDATION**

As the submission does not justify any new pediatric indications and does not indicate changes to the pediatric posology or target age groups and does not raise any new safety concerns, no regulatory action is recommended in the context of Article 45 review.

When the ICD-11 is released, and gives grounds, the MAH is encouraged to harmonise the indication terminology in the concerned Member States through appropriate variation procedures.

Therefore, the Rapporteur recommends that no further action required.

III. **INTRODUCTION**

Only Iroko submitted only one listed ‘completed pediatric study’ for indomethacin, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for pediatric use. – However, in all Iroko’s submission is a file with 55 references, most of them published reviews or clinical articles that do not serve the objective of Article 45 procedures to capture available original research data to improve pediatric sections of Product Information and to promote the evidence based pediatric use of medicinal products.

A short critical expert overview was also provided.

The MAH proposed the following regulatory action: modification of indication in section 4.1 to include:

- moderate to severe juvenile idiopathic arthritis.

For clarification, the current CCDS includes the indication:

- moderate to severe juvenile rheumatoid arthritis.

In Europe, the use of indomethacin in juvenile rheumatoid/idiopathic arthritis is approved in pediatric patients 2 years of age or older in Austria and Portugal; in France in children over 15
and in Spain in children over 14 years of age. – In Switzerland, only the sustained release formulation is approved so a pediatric indication is not applicable.

In addition, the following documentation has been included as per the procedural guidance:

– a line listing, and
– an annex including SPC wording of sections 4.1 and 4.2 related to the pediatric use of the medicinal product, and related PL wording

According to the Best practice guide Article 45 – paediatric regulation EU work sharing procedure (CMDh/037/2009/Rev 4, February 2012), the aim of Article 45 procedure is to make the information on the use of medicines in the pediatric population available for all health care professionals and patients (or parents).

According to the Recommendations on submission and assessment in paediatric work sharing (CMDh/141/2009/Rev2, March 2013), Article 45 is not expected to be a full harmonisation process. Where differences are identified in the pediatric aspects of product information, a recommendation can be made in the assessment report that the MAH achieve harmonisation through use of appropriate regulatory procedures. However, it should be possible to recommend consistent wording for existing indications and posology in the SmPC common to MS.

It is not the aim of Article 45 or 46 procedures to remove existing paediatric indications for products which are already in clinical use in particular member states. Removal of indications, for example if there is new evidence regarding safety, should be considered by individual member states unless there has been prior agreement by CMDh or through another regulatory procedure.

If appropriate, member states should consider referring the matter to CMDh or requesting a formal referral procedure to achieve harmonisation of the SmPC throughout the Community.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

The studies accepted for review were performed in the 1960s and 1970s and information on the pharmaceutical formulation is not available, other than that capsules and suspension were used. However, the suspension was supplied by Merck Sharp & Dohme.

Pediatric formulations have been available as suspension and suppositories. The MAH is currently not marketing suspension or the 50 mg suppository.

IV.2 Non-clinical aspects

1. Introduction

The MAH submitted four unlisted non-clinical publications that were considered too distantly related basic research to have any practical impact on this procedure (see Error! Reference source not found., under Non-clinical research). These reports were excluded from this review.

The MAH did not submit any extended synopses.

2. Non clinical studies

N/A
3. Discussion on non-clinical aspects and conclusion

N/A

IV.3 Clinical aspects

1. Introduction

The MAH submitted altogether 55 published references and regulatory documents (Error! Reference source not found.). However, only one publication can be considered to be a completed pediatric study in the meaning of Article 45 of Regulation 1901/2006 (included in the original line listing). In addition, one unlisted clinical study provided clinical trial data.

The MAH submitted the following listed report:


The MAH submitted the following unlisted report:


In addition, the MAH submitted 7 unlisted publications on pharmacokinetics, 26 unlisted reviews and 11 unlisted clinical articles. Three submitted articles were unrelated to the topic. Publications on pharmacokinetics were excluded, because they were not pediatric, were reviews or abstracts or concerned an intravenous formulation. Reviews and clinical articles such as case reports and non-pediatric papers were not considered to represent completed pediatric studies in the meaning of Article 45, and were excluded.

The MAH did not submit any extended synopses.

Just for the record, the following listed study report was not submitted:


  o This prospective randomised controlled trial comparing rectal indomethacin with placebo was performed in children. 30 children aged seven years and over undergoing open appendicectomy were given suppositories of either indomethacin 2 mg/kg or placebo. Suppositories were given at the conclusion of surgery and again 12 and 24 hours later. All children were given morphine by a patient-controlled analgesia pump. After 36 hours, children given indomethacin had used 0.51 (SD 0.34) mg/kg, and children given placebo 0.91 (SD 0.46) mg/kg (P < 0.02). Pain scores measured with a visual analogue scale, sedation scores and the incidence of vomiting were similar in both groups. Children given indomethacin suppositories used 44% less morphine than children given placebo, and at the same time obtained similar postoperative analgesia.
2. Clinical studies


➤ Summary

Ketoprofen (Orudis; Maybaker), whose use has not previously been reported in children, was compared with indomethacin in a double-blind crossover trial in 30 children with juvenile chronic arthritis. Both drugs proved to be safe and effective analgesics and anti-inflammatory agents although indomethacin emerged as the preferred drug. Perhaps higher doses of ketoprofen would be safe and more effective. Side-effects were few and mild. The problems of patient compliance and the assessment of pain in children are discussed.

A wide range of antirheumatic drugs is currently available. Only a limited number of these have been tried in children. We have used ibuprofen with disappointing results, whereas aspirin and indomethacin have proved most useful. The occurrence of side-effects and variations in individual responsiveness has necessitated a continuous search for safer and more effective anti-inflammatory agents.

➤ Methods

• Objectives

Ketoprofen is a non-steroidal anti-inflammatory agent. It is a propionic acid derivative which has been shown to be effective and well tolerated in adults. This study represents the first report of its use in children. Thirty patients with juvenile chronic arthritis were studied in a double-blind cross-over trial in which we compared indomethacin with ketoprofen.

• Study design

Patients were seen every week. They were given 30 capsules on each occasion and were instructed to take their medication with breakfast and supper. They were requested to return all unused capsules in the original containers to provide a check on patient compliance.

Patient record cards were designed so that the history - but not the results of previous assessments - was available at each visit. Blind assessments were made each week at a morning clinic by the same observer at each of 6 visits. At the first visit, details of present and past history and medication were entered on the record card, together with the report of previous radiographs and the results of physical examination.

Investigations for blood sedimentation rate, hemoglobin level, platelet and white cell count including differential, serum biochemistry including urea and liver function tests, urinalysis, and stool examination for occult blood, were done at the commencement, crossover and end of the trial.

• Study population /Sample size

Thirty patients with juvenile chronic arthritis as defined by Ansell and Bywaters were included in the trial. The investigators excluded all children with a history of any of the known contraindications to either of the trial drugs such as gastro-intestinal disturbance, headache, dizziness, and renal insufficiency, those currently receiving gold, d-penicillamine or
corticosteroids, and those who were in a state of remission. None of the patients had ever received gold nor had any patient received corticosteroids during the previous 12 months.

Patients took part in the study after informed consent was obtained from the parent or guardian. The total duration of the trial was 5 weeks.

- Treatments

All anti-inflammatory therapy was discontinued for 1 week, during which time the patient was allowed to take paracetamol, and requested to record the amount taken. Thereafter an equal number of patients received indomethacin for 2 weeks followed by ketoprofen for 2 weeks, and vice versa. The sequence of administration of these drugs was randomized. Dosage: children weighing less than 20 kg took ketoprofen 25 mg twice daily and indomethacin 25 mg twice daily. Children weighing 20 kg or more took ketoprofen 50 mg twice daily and indomethacin 50 mg twice daily. The drugs were presented in identical capsules, each containing 25 mg.

- Outcomes/endpoints

Assessments at each visit were recorded on 2 sheets. Subjective data were based on answers by the patient and/or the parents to standard questions relating to the severity of pain ('How severe has your pain been during the last week?'), the duration of morning stiffness ('How long has morning stiffness lasted during the last week?'), the extent to which pain or stiffness interfered with function, general feeling of well-being, and symptoms interpreted by the patients as being due to the treatment. At the end of the trial the patients were requested to express a preference for either of the two drugs.

Objective measurements at each visit included an 'articular index'. This measured response on a 4-point scale to pressure and passive movement of a joint through maximum range as follows: 0 - no tenderness to palpation or pressure in the region of a joint; 1 - complains of pain, 2 - complains of pain and winces, and 3 - complains of pain, winces and withdrawal or cries. The following joints were tested: cervical spine and hips (passive movement only), temporomandibular joint, shoulders, elbows, wrists, fingers, knees, ankles, subtaloid, midtarsal and metatarsophalangeal joints. A knee score was derived from a similar 4-point scale for each of pain, stiffness, tenderness and swelling. Combined finger joint circumference (proximal interphalangeal joints) was measured using a plastic strain gauge.

Grip strength was assessed by squeezing a water-filled rubber bulb to which a glass tube, calibrated in atmospheric units, was attached. An average of 3 readings was used. The temporomandibular joint was also assessed using an S.S. White bite gauge. Walking time was assessed over a distance of 10 metres.

At the end of each 2-week period, patients were asked to express their impressions of the drug: 'Do you feel much better, better, no different, worse, or much worse?'

At the end of the trial they were requested to express their preference for either of the two drugs by comparing their general feeling of well-being during each period. A record was also kept of other symptoms such as fever, rash, splenomegaly or lymphadenopathy. The investigator also expressed his own preference based on impressions during each of the two periods.

A careful record was kept of any side-effects noted at the end of each week, and of the amount of rescue drug (paracetamol) taken. Rescue drug was prescribed according to age, and dosage varied from 5 ml (120 mg) to 10 ml of suspension or 1 or 2 tablets (500 mg each). Each dose was regarded as one unit.
• Statistical Methods

The sign test, the Wilcoxon signed-rank test, and the χ² test, were used to analyse the results. Where appropriate, Student’s t test was also used.

➢ Results

• Recruitment/Number analysed

Table I shows the number of patients who completed the trial in each drug sequence. One patient had to be disqualified because instructions for taking the capsules were not strictly adhered to. No patient withdrew from the trial.

• Efficacy results

A comparison of the efficacy of the two drugs using the x' test is shown in Fig. 1. It is evident that indomethacin emerged as the preferred drug for most variables tested. It proved significantly superior for pain (P<0.05) and morning stiffness (P<0.05), and its contribution to improvement in functional status approached significance when compared with ketoprofen. It seemed marginally better than ketoprofen in producing a general feeling of well-being.

<table>
<thead>
<tr>
<th>Table I: Patients Admitted to Study</th>
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<tbody>
<tr>
<td>Sequence</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>I-K</td>
</tr>
<tr>
<td>K-I</td>
</tr>
</tbody>
</table>

I = indomethacin, K = ketoprofen.

Variable results were obtained when the different knee scores were studied. Ketoprofen was clearly superior to indomethacin in reducing knee tenderness and swelling. On the other hand, indomethacin was preferred as an analgesic. There seemed to be little difference in their ability to reduce stiffness. When all the scores were considered together, indomethacin nevertheless emerged as the drug producing the best results for the total knee score.

Neither drug produced any significant improvement on grip strength, combined finger-joint circumference or range of movement of the temporomandibular joint during the short period of the trial. Although subjective as well as objective clinical improvement in joint symptomatology was noted, the improvement in the articular index was not significant. Both drugs reduced the walking time during the first 2 weeks, but a further reduction in walking time was only achieved in those patients receiving indomethacin during the second 2 weeks of the trial.

During the first 2 weeks a significantly greater amount of rescue drug was taken with ketoprofen than with indomethacin (p<0.05). This difference seemed to disappear during the second half of the trial so that there was no significant difference in the amount of rescue drug required for the two drugs for the total duration of the trial.
There was little to choose between the two drugs in their antipyretic effect, but the duration of the trial was too short and there were too few patients to assess the effect on other constitutional manifestations such as rash, lymphadenopathy and splenomegaly.

- Safety results

There were few side-effects attributable to the drugs (Table II) and when they occurred they tended to be mild and did not require stopping of the drugs. Neither drug produced significant changes in the hemoglobin level, white cell count, erythrocyte sedimentation rate, serum biochemistry or urine. Frank blood was noted in a stool from one patient. None of the patients had to be withdrawn from the trial as a result of any untoward effect of either drug.

![Table II: Side-Effects](image)


- Summary

Two hundred and twenty-three infants and children with rectal temperatures greater than 101 °F due to diseases commonly encountered in pediatric practice, were given indomethacin suspension, indomethacin placebo or acetaminophen elixir in a random coded manner according to prescribed dosage schedules. The mean temperature reduction in those groups treated with indomethacin and acetaminophen was statistically significantly better than placebo, and a significant difference in temperature reduction was found between indomethacin and acetaminophen with indomethacin being superior.

- Methods

- Objective

To study antipyretic effect of indomethacin and acetaminophen in a placebo controlled setting in pediatric population.

- Study design

Randomised placebo controlled trial.

- Study population /Sample size

Two hundred and twenty-three infants and children under the age of 14 years who had fever over 101 °F rectally were given a single dose of indomethacin suspension, indomethacin
placebo or acetaminophen. In all instances the fever was associated with diseases commonly seen in pediatric practice.

- **Treatments**

The medications were given from coded bottles, and indomethacin suspension and indomethacin placebo suspension were indistinguishable. Acetaminophen elixir was unchanged from its commercial form because of concern that disguising the preparation might change its pharmacologic action. Indomethacin suspension and placebo, 10 mg/5 ml was given at a dosage of approximately 1 mg/kg.

<table>
<thead>
<tr>
<th>Weight in pounds</th>
<th>Dosage</th>
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<tr>
<td>15 to 30</td>
<td>1 teaspoonful</td>
</tr>
<tr>
<td>30 to 50</td>
<td>2 teaspoonfuls</td>
</tr>
<tr>
<td>50 and over</td>
<td>3 teaspoonfuls</td>
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</tbody>
</table>

Indomethacin placebo suspension was given similarly. – Acetaminophen elixir, 12.0 mg/5 ml was given in a dosage of approximately 3 mg/lb.

<table>
<thead>
<tr>
<th>Age</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 year</td>
<td>½ teaspoonful</td>
</tr>
<tr>
<td>1 to 6 years</td>
<td>1 teaspoonful</td>
</tr>
<tr>
<td>Over 6 years</td>
<td>2 teaspoonfuls</td>
</tr>
</tbody>
</table>

- **Outcomes/endpoints**

Rectal measurement of temperature before medication was given and every half hour for 3 hours. Follow up and recording of side effects.

- **Statistical Methods**

Analysis of covariance and descriptive methods.

- **Results**

- Recruitment/ Number analysed

There were 76 patients in the indomethacin group, 72 in the acetaminophen group, and 75 in the indomethacin placebo group.

- **Baseline data**

Mean initial rectal temperatures were: indomethacin group, 102.5 °F; acetaminophen group, 103.3°; and indomethacin placebo group, 102.6°. Since these temperatures were found to be significantly different an analysis of covariance was utilized for comparison purposes.

- **Efficacy results**

The mean temperature reduction in those groups treated with indomethacin and acetaminophen was statistically significantly better than placebo, and a significant difference in temperature reduction was found between indomethacin and acetaminophen with indomethacin being superior.
Safety results

Patient acceptance of indomethacin suspension was adequate and the only side effects were drowsiness in 2 patients; one acetaminophen patient and none of the placebo patients manifested drowsiness after administration of the drug.


Failure to submit this small clinical trial is not considered to have any significant effect on this assessment.

3. Discussion on clinical aspects and conclusion

Although the use of indomethacin is not recommended for children in the USA it has been used with benefit elsewhere. The occasional side-effects of headache, nausea, vomiting, abdominal pain, and the less common elevation of blood urea (particularly in those patients concurrently receiving gold or penicillamine) led Bhettay and Thomson to examine the merits of ketoprofen as an alternative anti-inflammatory agent.

Assessments showed that all patients improved, although some only slightly. None had deteriorated compared with the pre-trial assessment, suggesting that both drugs had some therapeutic benefit. The results showed clearly that both drugs relieve pain and improve morning stiffness, the ability to walk and the patients' general well-being. Indomethacin had a significantly greater analgesic effect, and seemed to be more beneficial than ketoprofen in some of the variables studied. This was independent of the treatment sequence.

Both drugs were well tolerated and appeared safe, judging from the paucity and mildness of the side-effects noted during the trial. The infrequency of side-effects in children on indomethacin has been of interest, in contrast to the much greater frequency of side-effects in adults.

The study led the researchers to conclude that both ketoprofen and indomethacin are useful anti-inflammatory agents. Improvement seemed notably but not significantly better with indomethacin. Both drugs appeared to be safe. In view of the lack of previous experience with ketoprofen in children, the chosen dosage was arbitrary. It is possible that a higher dose is safe and may represent a fairer trial of ketoprofen.

This study of Brewer was the first double blind placebo study carried out to compare the antipyretic effect of indomethacin and placebo. In addition, acetaminophen was included in the comparison. Studies by Colgan and Mintz (1957) showed acetaminophen to be equal to aspirin in antipyretic activity.

Even though the colour of the acetaminophen elixir was clearly different from the indomethacin and placebo suspensions, all bottles were coded and given in a random manner to prevent bias.

Indomethacin proved an effective antipyretic agent at all levels of fever, but in particular, it showed the greatest effect in those patients with extremely high temperatures. This is important because of the potential use of indomethacin in those patients with high fever and fever resistant to other antipyretics, and in those whose clinical condition requires a more effective antipyretic agent.
The data in this study tend to support our observation that dramatic antipyretic response resulted from indomethacin. Although indomethacin may have significant side effects another look should be given to its potential usefulness in pediatric patients who have significant pyrexia.

The MAH states that besides the controlled clinical trial by Bhetay and Thomson (1978), no further controlled clinical studies on efficacy and safety of indomethacin in children or adolescents with juvenile rheumatic/idiopathic/chronic arthritis has been published in that search interval.

In conclusion, very limited and historical research data was submitted to this appraisal. Considering the proposed regulatory action, the submitted data does not contribute solid scientific justifications. The MAH proposes to add a pediatric indication ‘juvenile idiopathic arthritis’ or to amend the existing ‘juvenile rheumatoid arthritis’ to the proposed wording.

From the published literature, it appears that juvenile idiopathic arthritis is being increasingly internationally accepted as the umbrella term for several clinical presentations of pediatric rheumatic disease. It seems also quite likely that the next international classification of diseases ICD-11, will include juvenile idiopathic arthritis instead of juvenile rheumatoid arthritis. However, the ICD-11 is still in beta phase, and the 11th revision is due to be published by 2017.

The current product labeling reads:

4.1 Indications

Moderate to severe juvenile rheumatoid arthritis

4.2 Dosage

JUVENILE RHEUMATOID ARTHRITIS (PEDIATRIC USAGE)

For children two years of age or older with juvenile rheumatoid arthritis, INDOCID may be started at a dosage of 1–2 mg/kg/day in divided doses b.i.d. or t.i.d., and increased weekly as needed to a maximum of 3 mg/kg/day. Maximum daily dosage should not exceed 200 mg/day or 3 mg/kg/day, whichever is less. Limited data are available to support the use of a maximum daily dosage of 4 mg/kg/day or 200 mg/day, whichever is less. As symptoms subside, the total daily dosage should be reduced to the lowest level required to control symptoms, or the drug discontinued.

The MAH proposes the following text:

4.1. Therapeutic indications

Moderate to severe juvenile idiopathic arthritis

4.2. Posology and method of administration

Children and adolescents with juvenile idiopathic polyarthritis

For children 2 years of age or older with juvenile idiopathic arthritis, [TRADENAME] may be started at a dosage of 1–2 mg/kg/day in divided doses b.i.d. or t.i.d., and increased weekly as needed to a maximum of 3 mg/kg/day. Maximum daily dosage should not exceed 200 mg/day or 3 mg/kg/day, whichever is less. Limited data are available to support the use of a maximum daily dosage of 4 mg/kg/day or 200 mg/day, whichever is less. As symptoms subside, the total daily dosage should be reduced to the lowest level.
required to control symptoms, or the drug discontinued. Safe conditions for use in children under 2 years of age have not been established.

The efficacy and safety in the other indications have not been studied in children and adolescents. For this reason, use in patients under 18 years of age is not recommended.

4. Relevant pharmacovigilance information

The safety profile of indomethacin is well established. Several unlisted references submitted underscore the gastrointestinal toxicity also in patients with juvenile idiopathic arthritis, but do not add weight to the evidence, because the papers include uncontrolled studies, non-pediatric data, case histories etc.

The Reference Safety Information of the MAH already covers the main concerns: ‘Gastrointestinal reactions which occur most frequently are nausea, anorexia, vomiting, epigastric distress, abdominal pain, constipation, and diarrhea. Others which may develop are ulceration - single or multiple - of esophagus, stomach, duodenum or small or large intestine, including perforation and hemorrhage with a few fatalities having been reported; gastrointestinal tract bleeding without obvious ulcer formation; and increased abdominal pain when used in patients with preexisting ulcerative colitis. Reactions which occur infrequently are stomatitis; gastritis; flatulence; bleeding from the sigmoid colon, occult or from a diverticulum; and perforation of preexisting sigmoid lesions (diverticula, carcinoma). Rarely, intestinal strictures (diaphragms) and intestinal ulceration followed by stenosis and obstruction has been reported. Other gastrointestinal side effects which may or may not be caused by indomethacin include ulcerative colitis and regional ileitis.’

The MAH submitted a Periodic Safety Update Report (PSUR) covering all indomethacin containing single ingredient products for the period from 22 June 2009 to 21 June 2012 (Data Lock Point).

Iroko acquired rights to market indomethacin from Merck & Co, Inc. in most countries around the world in 2007. The divestiture of the individual licenses is on-going, and until completed, Merck and Iroko will exchange safety data and produce common PSURs. Since May 2011, the responsibility for the compilation of each PSUR (including addendum reports and summary bridging reports) for Indocin capsules, sustained release capsules, oral suspension and suppositories and PSURS including all formulations of Indocin reside with Iroko. This PSUR was written by Iroko and summarises the safety data from all territories regardless of the current Marketing Authorisation Holder (MAH) for the above mentioned period.

Iroko Products currently hold the Marketing Authorisation for indomethacin in 22 countries worldwide. In 5 countries Marketing Authorisation transfers from Merck are pending.

No changes to the Reference Safety Information (Indocid™ Worldwide Product Circular, dated August 2006) were made during the PSUR period.

During the period of the PSUR, the exposure to indomethacin was approximately 3.264.924 patient-months of treatment.

During the period of this PSUR, a total of 235 medically confirmed case reports (all initial) were received worldwide. Of these, 56 were serious unlisted, 61 serious listed, 66 non-serious unlisted and 52 non-serious listed. In addition, 17 medically unconfirmed ICSRs were received from non-healthcare professionals. Cumulatively, the MAH have received 453 serious and unlisted adverse drug reactions.
· Pediatric data

There were only seven cases concerning the use of indomethacin in patients aged under 18 years of age:

- Case IND1-TW-2010-0049 reported an infant placed on therapy with indomethacin capsules dissolved with beer, who died following severe oliguria and sepsis. This idiosyncratic route of administration is completely outside the RSI instructions. There was no reason to conclude that similar routes of administration have been used previously.
- An 8-year-old who developed eye tics, headache and vomiting was presented in case IND1-US-2010-0075.
- Case IND1-US-2011-0035 concerned eleven infant patients who developed necrotising enterocolitis.
- Pneumoperitoneum and ileal perforation in a 4-day-old male was presented in case IND1-JP-2012-0006.
- One case reported acute liver failure in a 9-year-old patient (IND1-UK-2009-0015).
- Case IND1-FR-2011-0050 presented a 10-year-old who developed acute gastroenteritis following collective food poisoning with Salmonella. She was significantly dehydrated and experienced acute renal failure requiring dialysis.
- A 17-year-old female patient developed a headache one day after starting indomethacin. Five days later, she developed a migraine (IND1-US-2010-0047). Dechallenge was positive. The investigator considered that the event was possibly related to indomethacin. However, considering the patient’s medical history (migraines lasting for 11 months), concomitant use of methotrexate, and the fact that migraine persisted more than a week even after indomethacin was stopped, the causal relationship between migraine and indomethacin in this case is unlikely.

Review of these reports did not yield any new significant safety information on indomethacin usage in this patient population.

With regards to pediatric use, the RSI states that safe conditions for use in children under 2 years of age have not been established. Children should be monitored closely and periodic evaluations of liver function should be performed at appropriate intervals. Cases of hepatotoxicity including fatalities have been reported. MAH considers this wording considered sufficient.

According to the MAH, the data within this PSUR supports the conclusion that the overall benefit-risk balance for indomethacin is unchanged and that there are no recommended changes to the Reference Safety Information.

During the period of this PSUR review it was assessed that there were no rationale for urgent or expedited updates to the Reference Safety Information.

There were no significant potential safety signals. According to the MAH the data contained within this PSUR supports the conclusion that the overall benefit-risk balance for indomethacin tablets remains unchanged and that there are no recommended changes to the Reference Safety Information.
V. MEMBER STATES’ OVERALL CONCLUSION AND RECOMMENDATION

Very limited and only historical research data was submitted to this assessment. Only two clinical studies and PSUR data were considered relevant in the context of Article 45 review. Considering the proposed regulatory action, the submitted data does not contribute solid scientific justifications. The MAH proposes to add a pediatric indication ‘juvenile idiopathic arthritis’ or to amend the existing ‘juvenile rheumatoid arthritis’ to the proposed wording.

Certainly, the submission does not support opening a new pediatric indication for the product. However, this is not intended either, as the proposed change from rheumatic to idiopathic is merely a reflection of evolving classification terminology.

From the published literature, it appears that juvenile idiopathic arthritis is being increasingly internationally accepted as the umbrella term for several clinical presentations of pediatric rheumatic disease. It seems also quite likely that the next International Classification of Diseases ICD-11, will include juvenile idiopathic arthritis instead of juvenile rheumatoid arthritis. However, the ICD-11 is still in beta phase, and the 11th revision is due to be published by 2017.

The submitted material does not indicate any changes in the established pediatric posology, and does not help to resolve the differences in national target age groups.

The submitted material does not indicate changes to the established pediatric safety profile.

➢ Overall conclusion

The Rapporteur concludes that as the submission does not justify any new pediatric indications and does not indicate changes to the pediatric posology or target age groups and does not raise any new safety concerns, no regulatory action is recommended in the context of Article 45 review.

When the ICD-11 is released, and gives grounds, the MAH is encouraged to harmonise the indication terminology in the concerned Member States through appropriate variation procedures.

Three Member States endorsed the overall conclusion of the Rapporteur by Day 85 of the procedure. One Member State suggested that the indication should have been changed immediately. The Rapporteur considered that the Member States can request such variations regardless of the outcome of this process. No further comments were received.

As no supplementary information was requested, the preliminary AR is also the final AR.

➢ Recommendation

No further action required.
VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

<table>
<thead>
<tr>
<th>Country</th>
<th>MAH</th>
<th>Product name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT</td>
<td>Iroko Products Limited, One Silk Street, London, EC2Y 8HQ, UK</td>
<td>Indocid 25 mg Kapseln</td>
<td>25 mg</td>
</tr>
<tr>
<td></td>
<td>Iroko Products Limited, One Silk Street, London, EC2Y 8HQ, UK</td>
<td>Indocid retard 75 mg Kapseln</td>
<td>75 mg</td>
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<td>ES</td>
<td>Iroko Products Limited, One Silk Street, London, EC2Y 8HQ, UK</td>
<td>INACID 25 mg cápsulas</td>
<td>25 mg</td>
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<td>Iroko Products Limited, One Silk Street, London, EC2Y 8HQ, UK</td>
<td>INACID RETARD cápsulas</td>
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<td></td>
<td>Iroko Products Limited, One Silk Street, London, EC2Y 8HQ, UK</td>
<td>INACID Supositorios 100 mg</td>
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<td>FR</td>
<td>Iroko Products Limited, One Silk Street, London, EC2Y 8HQ, UK</td>
<td>INOCID 25 mg, gérule</td>
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<tr>
<td></td>
<td>Iroko Products Limited, One Silk Street, London, EC2Y 8HQ, UK</td>
<td>INOCID 50 mg, suppositoire (not commercialized)</td>
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<td>Iroko Products Limited, One Silk Street, London, EC2Y 8HQ, UK</td>
<td>CHRONO-INDOCID 75 mg, gérule</td>
<td>75 mg</td>
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<td>INOCID 100 mg, suppositorie</td>
<td>100 mg</td>
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<td>PT</td>
<td>Iroko Products Limited, One Silk Street, London, EC2Y 8HQ, UK</td>
<td>INOCID-cápsulas de liberacao prolongada-75 mg</td>
<td>75 mg</td>
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<td>INOCID-supositorio-100 mg</td>
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<td>CH (Non-EU)</td>
<td>Future Health Pharma GmbH Guyer-Zeller-Strasse 10, CH-8620 Wetzikon, Switzerland</td>
<td>Indocid Retard 75 mg</td>
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